JOINT DISCUSSION No. 7.

Section for the Study of Disease in Children and Section of Medicine.

Chairman—Dr. J. D. ROLLESTON (President of the Section for the Study of Disease in Children).

DISCUSSION ON THE SERUM TREATMENT OF SCARLET FEVER.

Dr. E. W. GOODALL.

IN initiating a discussion on the serum treatment of scarlet fever, there are two points which I wish to mention before coming to the subject-matter proper to the discussion; the first is that I cannot claim to deal with the question in an authoritative manner, because before I had thoroughly made up my mind as to the efficacy of the treatment I ceased to enjoy first-hand opportunities for so doing. The second, and more important, is that I shall assume that the hæmolytic streptococcus of George and Gladys Dick is the true bacterial cause of the disease, for I am of the opinion that the Dicks' claim has been established. If there be any clinician who, reporting favourable results from the serum, yet denies that the above-mentioned streptococcus is the cause of scarlet fever, he must explain his success by some other reason than that advanced by those who believe in the specificity of the micro-organism.

Now clinicians, in endeavouring to ascertain by personal observation, and by statistical results, the value of the serum treatment of scarlet fever, are not so favourably placed, at any rate so far as those practising in this country are concerned, as were those who were called upon to pronounce an opinion on the antitoxin treatment of diphtheria upwards of thirty-two years ago. At that time, in London, the type of that disease was very severe, as the fatality of the cases admitted to hospital was over 30 per cent., so that it was comparatively easy in a few weeks to come to a decided conclusion on the value of any sort of treatment. But with scarlet fever the case is different, because for some years past the type of the disease has been very mild; consequently a larger number of cases, and a more lengthy period are necessary in order to pronounce a just judgment. The fatality of the cases treated in the Asylums Board Hospitals has only once been above 2 per cent. since 1910, and that was in 1916; at the North-Western Hospital, of which I had charge for the last ten years of my service, the fatality was 1·01 per cent. for the year 1925. There is not much room, therefore, for improvement in treatment so far as the saving of life is concerned, though, of course, the superiority of one method of treatment over another must, and may, be demonstrated in a non-fatal, or slightly fatal, disease by other results than a fall in the case mortality. There is another point which makes it more difficult to arrive at the truth in the case of scarlet fever than in that of diphtheria, namely, that whereas diphtheria in the great majority of cases is a toxæmia pure and simple, in scarlet fever it is admitted that there is a bacteriæmia as well as a toxæmia, and it is often a bacteriæmia of the same micro-organism as produces the toxæmia. In diphtheria, if there is an additional bacteriæmia, it is rarely, if ever, of the *Corynebacterium diphtheriæ*. Further, I understand that those bacteriologists who are responsible for the making of the scarlatinal antiserum do not claim that the serum is antibacterial as well as antitoxic. In a double pathology such as occurs in those very cases of scarlet fever which are to be blamed for most of the deaths—the anginous or septic cases—it is not easy always to decide whether the symptoms are due entirely to septicæmia, or whether toxæmia is also present.

152 Goodall: *Discussion on the Serum Treatment of Scarlet Fever*

It appears to me that the following are the points which can most usefully be considered in this discussion:—

(1) Is the treatment by the new serum better than any other treatment?

(2) If it is, how is its superiority shown?

(3) Can any difference be made out, in respect of results, between the toxæmic and the septic symptoms?

(4) What is the correct dosage?

As already said, it is difficult in this country, at any rate in London, to demonstrate any improvement in the case mortality because of the natural mildness of the disease. So far as I have been able to ascertain from published accounts, only one serious claim has been put forward that there has been any such reduction, viz., that by Cushing, of Montreal. Several observers have stated their belief in the efficacy of the serum, but on other grounds. Even in some cities of the United States there has been a comparatively high fatality during recent years. No statement has been made in published reports on the treatment in respect of the fatality rate, so that it is to be presumed that no reduction was observed; for example, 160 cases, stated to be severe, treated by Woody, of Philadelphia; 35 by Selinger, of Washington, D.C.; an unstated number by Birkhaug, of New York. There have been some high fatality rates amongst hospital cases in New York. Thus, at the Willard Parker Hospital the rates per cent. were as follows for the five years 1919-1923—5·9, 12·0, 8·4, 8·2, and 4·6. Serum treatment was begun as a routine measure in March, 1925, but I have not seen any statement as to the effect, if any, on the fatality rate. Scarlet fever has been extremely severe recently in Eastern Europe, and in China. In the former country the specific serum has apparently not yet been used, at any rate extensively; but in the latter it was tried at the "Government Isolation Hospital," at Peking, and found to be of little value in the toxic form of the disease. Later, a serum produced by a different method proved to be of some use. Cushing, of Montreal, states that at the Alexandra Hospital, Montreal, the scarlet fever fatality was over 5 per cent., but that it had been falling, and that in 1923 it was 3·2 per cent. In 1924, when serious cases were treated with convalescent serum, the fatality was 2·0 per cent. Writing in August, 1926, he stated that since antitoxic serum had been more generally used, 500 out of 800 cases had been treated with it and that there had been ten deaths, a fatality of 1·2 per cent. In eight of these cases, however, death was not due to scarlet fever, and in the other two the serum was not given until the ninth day. With the exception of this series of cases, I have not been able to find any evidence of a reduction of the fatality, such as was the case in diphtheria immediately after the introduction of the serum treatment, and those clinicians who have come to the conclusion that the treatment is valuable have done so on other grounds. Amongst these must be mentioned Harries, of Birmingham, Thomson, of London, and Hutchinson, of Dublin, besides the American observers referred to above, to whom must be added Park, of New York and Gordon, of Chicago. The principal grounds on which they base their opinion are rapid fall of temperature, disappearance of delirium, rapid subsidence of the faucial inflammation, quicker fading of the rash than is usual, and lessening of the amount of desquamation: briefly, a more rapid improvement in the condition of the patient than is met with in other methods of treatment. It has been noticed, however, by more than one physician, that now and again there is a case that does not respond. All agree that, as with diphtheria antitoxin, the earlier the remedy is given the better and the surer the result, and that if it is administered late, on the fifth day or after, favourable effects are hardly to be expected.

My own personal experience has been very limited. At the North Western Hospital we began to treat a few selected cases towards the close of 1925. I found it very difficult in that desultory way to come to any definite conclusion; moreover,

the cases which were being admitted at that time were very mild. I remember having a series of 300 admissions without a death. About April, 1926, we began to treat rather more cases of a more severe type, and were obliged to make some selection, for we were not supplied with an unlimited amount of serum. Up to the time I left the hospital in August, I had personally observed and made notes upon fifty-six cases. This is far too small a number upon which to make a final pronouncement, and I can give only a preliminary impression. Patients in the more severe cases received serum; a few cases were mild on admission, but became worse in the course of a day or two and then were treated.

Of the fifty-six patients four died, but not one of them from scarlet fever, pure and simple, and uncomplicated.

The first was a boy, aged 1 year, who had severe faucial inflammation and bronchitis. 25 c.c. were given on the third day and 20 c.c. on the fourth. There was no improvement at all and he died on the fifth day. Bronchitis was chiefly responsible for his death.

The second case was that of a boy, aged 5 years, with toxic symptoms. He received 20 c.c. on the fourth day and 25 c.c. on the fifth. Two days later there was an improvement; but septic complications, dacryocystitis and otitis media developed, and he died on the fifty-second day from cerebral abscess.

The third fatal case was that of a boy, aged 7. He received 50 c.c. on the third day, but showed no improvement. Otitis, mastoiditis and endocarditis supervened, and he died on the twenty-sixth day.

The fourth case was that of a woman, aged 28, who had been confined four days before admission and two before the rash appeared. She exhibited very severe toxic and septic symptoms; the latter were due to uterine infection, as there was no exudate on the fauces. She was given 45 c.c. on the second day and 45 c.c. on the third. Her condition improved on the fourth day so far as the toxic symptoms were concerned. She died on the thirteenth day. A post-mortem examination was refused, but I have no doubt that she had pyæmia, of which the focus was in the uterus.

Twenty of the patients were under 5 years of age and and thirty-eight were under 10. Forty-one patients received serum during the first three days of their illness.

I have not witnessed any of the remarkable cases described by one or two observers, toxic cases in which all the symptoms abated within twenty-four hours; but amongst my cases there was none that was purely toxic and uncomplicated. If the four fatal cases are excluded, the fifty-two cases comprised two with combined toxic and septic symptoms, thirty-three septic and seventeen benign cases. By septic I mean those cases in which the faucial lesion is a prominent feature of the attack, scarlatina anginosa. I do not mean that all the septic cases were necessarily severe, but those which were not might readily have become so.

Two cases are described as being both toxic and septic:

(1) A girl aged four years and (2) a man aged 34. On the third day of the disease 60 c.c. were given in the first case and 85 in the second. Both patients were much better the next day. The girl recovered without any complication, the man suffered from slight rheumatism.

The following table is compiled from notes made on the progress of the cases which I personally observed:—

Exclusive of fatal cases	Day of disease on which serum was first given: number of cases					
	1	2	3	4	5 and over	Total
Much better next day ...	4	12	5	2	1	24
Better next day ...	3	3	3	2	—	11
Better two days after ...	—	2	5	—	1	8
No improvement ...	—	—	1	3	5	9
Total ...	7	17	14	7	7	52
Complications ...	—	2	6	4	2	14

154 Goodall: *Discussion on the Serum Treatment of Scarlet Fever*

By " no improvement " is meant no improvement that could be ascribed to—and would have been expected from—the use of the serum; the patients gradually improved in the same manner as under the ordinary forms of treatment.

The occurrence of complications was as follows (the four fatal cases are excluded): First-day cases, *nil*; second day, two, one of rheumatism and cervical adenitis, and one of otitis media; third day six, two of nephritis, three of otitis, and one of rheumatism, an old heart case; fourth day, four, one of otitis and cervical abscess, one of nephritis, one of rheumatism, and one of broncho-pneumonia; fifth day and over, two, one of otitis and one of albuminuria (? nephritis).

From the results recorded in this table I came to the conclusion that a *primâ facie* case had been made out in favour of the serum. The results, so far as they go, support the opinions expressed by other clinicians that the earlier the treatment is begun, the better the result and the smaller the likelihood of complications.

I noticed that in some of the cases with marked faucial inflammation, while the general symptoms improved quickly, the throat lesion was slower in clearing up.

Twenty-four of the patients underwent an attack of serum-sickness, and in one case there was an abscess at the site of injection. In only one case was the attack severe. The serum was, I understood, an unconcentrated serum, that is, it had not been deprived of its euglobulin and albumin.

It is to be remembered that successful results have been claimed for multivalent antistreptococcal serum in scarlet fever long before the new serum was introduced. I have seen what I believed to be the beneficial results of a multivalent serum. Whether in those cases the good results were due to the accidental presence of the special hæmolytic streptococcus in the mixture of bacteria which was used as the antigen for producing the antiserum, or whether they were due to what is known as protein therapy, is uncertain; probably the former, for in my successful cases I never saw one in which there was a rigor or any shock. On the other hand, I have met with some remarkably favourable results of the treatment of typhoid and para-typhoid fever with both an antiserum and a vaccine. Such results could not have been due to any specific action. In several of the cases a rigor or shock symptoms occurred. In the present series of cases protein therapy may, in my opinion, be excluded.

There is not sufficient evidence to draw any conclusion as to the question of an antibacterial action of the serum. Experiments on animals go to show that the serum supplied up to the present time has no antibacterial value.

As regards dosage, we were told frankly by Dr. O'Brien that the dosage was uncertain, because there was no certain method of standardization. We gave the serum in doses of 20 to 100 c.c., mostly in single doses (forty-five cases). The most frequent dose was 50 c.c. From my experience of these cases, which I admit to be very limited in number, I should recommend that 30 c.c. should be given in cases, if not severe, seen on the first day, but 50 c.c. in severe cases. Twenty c.c. should be added to the dose for every additional day, and according to the severity of the attack. Thus, a severe case seen on the second day would require 70 c.c., and on the third up to 90 c.c. It is advisable to give the dose in one injection only. In nearly all my cases the injections were given intramuscularly; none was given intravenously, but this method should be used in the severe toxic cases where possible. The serum is antitoxic only, and not antibacterial. As scarlet fever is not infrequently also a septicæmia, the cases in which the symptoms are chiefly due to septicæmia will not, presumably, receive benefit.

I do not advise giving the serum in mild cases, as the serum-sickness which may follow may be more unpleasant than the attack of scarlet fever. But every case should be carefully watched, and if it shows signs of becoming worse should then be treated with serum.

So far as I am aware, the serum has not been given in this country by unit-dosage, as in the United States. A unit has been defined as that amount of serum which will neutralize 100 skin-test doses of toxin, and a skin-test dose as 0·1 c.c. of a 1 in 1,000 dilution of the toxin. But as the methods of standardizing the toxin and the serum have so far proved very unsatisfactory, the unit system of dosage has not been adopted in this country. In the United States the dosage has been from 2,000 to 10,000 units. In volume these doses would be from 5 or 6 to 50 or 60 c.c.

I hope that those who follow me in this discussion, and who have enjoyed a larger experience than mine, will deal chiefly with the following questions: (1) Has their experience enabled them to form a decided opinion as to the value of the treatment? (2) If their opinion is favourable, what is the effect of the serum, if any, in respect of the septic element in the disease and of its complications? and (3) What is the dosage and what are the conditions by which it is influenced?

Dr. R. A. O'Brien.

As my own clinical opportunities are limited, I recently referred the three important questions before us to the superintendents of three hospitals—all outside London—because I anticipated that experienced London clinicians would be present at this meeting and also because the disease in the north has probably been of a more severe type than the very mild type commonly seen in London. The three superintendents generously gave me permission to quote their opinions and experience this evening.

In the *Edinburgh Medical Journal*, December, 1926, Dr. Benson, of the City Hospital, Edinburgh, described his results in the treatment of 100 cases of scarlet fever. He concludes that: "The administration of antitoxic serum within the first forty-eight hours of the disease has a very favourable influence on the specific toxæmia of scarlet fever. In relieving the more urgent symptoms of the acute stage it undoubtedly renders the patient more comfortable.

"There are indications that the liability to subsequent complications is diminished.

"The administration of serum even on the first day of illness apparently does not act as an absolute safeguard against the subsequent development of complications of septic type in convalescence.

"In toxic cases of scarlet fever, serum should be administered either intravenously or intramuscularly at the earliest opportunity and the dose repeated if necessary."

Dr. Benson has since treated between two and three hundred patients with English concentrated serum. The dose was usually 10 c.c.—exceptionally 20 c.c. He says: "The former dose exercises a definitely favourable effect in the mild and moderate cases. The serum does not seem to touch the septic type of the disease. Serum rashes were troublesome. Serum therapy is certainly worth while, more particularly in the sharper cases. I am not, however, prepared to discharge my patients in the third week of convalescence merely on the strength of serum treatment."

Dr. Harries, of the City Hospital, Birmingham, writes: "We have used scarlet fever antitoxin for about eighteen months, and concentrated antitoxin as a routine in all except the mildest cases for six to eight months. Serum sickness is infrequent and trifling when it occurs. A dose of 10 c.c. is sufficient in the average case.

"There is some reason for hoping that serum will diminish complications and will reduce the necessary stay in hospital. If it has these effects, it is obvious that the money spent on antitoxin would be well spent.

"It is unnecessary to reiterate the well-known effects of scarlet fever antitoxin on the toxæmia of scarlet fever. The more striking the case the more striking are

the results of treatment with scarlet fever antitoxin. The problem of scarlet fever is, in my opinion, one of late morbidity, and it is impossible to forecast what complications a patient with a mild initial attack may develop in the second or third week. Only a long series of cases treated and untreated with serum can establish whether serum treatment does decrease the incidence of late complications.

"I found no direct curative influence on the septic complications of scarlet fever. A serum on the market, stated to be antibacterial as well as antitoxic, has, in my hands, given no antibacterial results.

"To sum up, I have no personal doubt as to the curative value of scarlet fever antitoxin, and should regard it as a failure of my duty if I withheld antitoxin from a severe case of scarlet fever.

"With regard to prophylaxis, we have never yet known a child who has been rendered Dick-negative by antitoxin to contract scarlet fever, although repeatedly exposed. We have, however, seen children, whose passive immunity had waned and who had become Dick-positive, contract scarlet fever after exposure."

Dr. Harries in a later letter adds that in fifty successive patients treated with concentrated serum there were no septic complications. Thirty-three patients showed no symptoms of serum sickness; amongst those with symptoms none were in any way severe, and all the patients were ready for discharge in thirty days. At present all clinically severe cases receive serum; of the others every alternate patient receives serum.

Dr. Rundle (Liverpool City Hospital) has used serum in about one hundred cases. Five deaths occurred. "The cases were selected for treatment by reason of their 'toxicity,' and many of them would, in our opinion, have succumbed without the serum. The hundred cases includes, however, about twenty-five of the septic variety, coming late under treatment and deriving no obvious benefit from the antitoxin. The deaths, with one exception, occurred amongst this 'septic' type. Antitoxin is of no use once septic throat, adenitis, etc., have set in. The serum phenomena have been more intense than one finds with antidiphtheria serum. Although one expects a dramatic fall of temperature and general alleviation with serum in the toxic cases, there is no guarantee that the usual complications will not arise. We have had some severe suppurative conditions in patients who had serum some days previously."

The experiences of these three observers apparently agree fairly closely with the general experience of clinicians in America.

The question of specificity and standardization of scarlet fever antitoxin arises directly from the important question of dose raised by Dr. Goodall. My colleagues, Dr. Parish and Dr. Okell, have kindly allowed me to show two tables from a paper which they have in preparation. From the first table it will be seen that when a sufficient dose of culture of the hæmolytic streptococcus of scarlet fever is injected intravenously into a rabbit, the rabbit almost invariably dies of the initial "toxæmia" or "septicæmia" in less than two days. Normal horse serum and non-specific antitoxin do not protect the rabbits, human convalescent serum does so to some extent; concentrated scarlet fever serum protects completely when given in a moderate dose. The most interesting part of the table is that relating to the use of the serum that has been issued commercially by many laboratories for many years past as antistreptococcus scarlet fever antiserum. This serum was a legacy from the period about 1902 when Marmorek, Gabritchewsky, Moser, Schick and others used the serum of horses injected with broth culture of streptococci obtained from the throats of scarlet fever patients for the treatment of scarlet fever. There is very little doubt, from their clinical records, that the serum they used at first had a definite therapeutic effect on scarlet fever. The serum later slowly

somewhat declined in favour because some workers failed to record any improvement in their patients after the use of the serum, and further, using large doses of the serum, they found that their patients often had severe serum reactions. The incidence of these serum reactions to-day has been greatly reduced by the well-known processes of concentration. Examination of some of the serum made by this method has shown that it has a definite but low amount of antitoxin in it.

Dr. Parish and Dr. Okell have shown that some of this serum was approximately half as strong as a high value concentrated scarlet fever antitoxin of to-day. Unfortunately, it does not seem to have occurred to anyone to use an obviously simple method of titrating this serum, i.e., to find accurately how much of this serum was necessary to protect from scarlet fever contacts exposed to infection. Had this been done, it is fairly certain that some of the serum in use could easily have been demonstrated to contain a very small amount of antitoxin and would have been replaced by the most potent serum then available.

The second table relates to some very recent work. A fascinating immunological puzzle concerns the relation of the hæmolytic streptococci to one another. The hæmolytic streptococcus of follicular tonsillitis and that of puerperal septicæmia cannot with any certainty be distinguished by the bacteriologist from the streptococci found in every scarlet fever throat. An obvious method of attack on this problem is to make toxins from the various organisms and test them on human beings, to see if the same patients are positive to all three toxins or negative to all three toxins. And, if so, to discover whether the positive Dick reaction is neutralized by anti-follicular tonsillitis antoxin or by anti-puerperal, anti-cellulitis, or other antitoxin.

Such a research has long been projected by Dr. Okell, and, as opportunity offers, is being carried through. But while waiting for the results of tests on human beings, Dr. Parish and Dr. Okell have carried out in rabbits the experiment indicated. It is remarkable that six strains of hæmolytic streptococci from patients suffering from puerperal septicæmia and two strains from patients with follicular tonsillitis, which promptly kill all the unprotected rabbits, fail to kill within three days any of the rabbits protected with scarlet fever concentrated antitoxin. The antigenic overlap amongst these hæmolytic streptococci must be very close, amounting perhaps to identity. It is reasonable to hope from these results that the homologous antitoxins, and also the concentrated scarlet fever antitoxin, may be of definite service in combating at least the first toxæmia or septicæmia of follicular tonsillitis, puerperal septicæmia and cellulitis, etc., caused by this same group of hæmolytic streptococci.

The question of *dosage* is closely linked with that of standardization. The various methods are well known, i.e., neutralization of toxin in the skin of human beings by measured quantities of antitoxin, similarly in goats, the determination of an adequate dose for passive immunity, the dose necessary for Schultz-Charlton blanching, and the rabbit protective dose. The determination of the prophylactic dose, i.e., one that will turn positive Dick reactors negative overnight and keep them negative during the incubation period of scarlet fever, has proved to be easy and supplies a method available in the hands of the hospital superintendent for titrating the serum he proposes to use, should he so desire. It is found that, with a good concentrated serum, this dose varies from 2 c.c. to 4 c.c. or 5 c.c. Such a serum will usually produce blanching when injected into an early scarlet fever rash in a dilution of upwards of $\frac{1}{1000}$.

CONCLUSIONS.

Concentrated scarlet fever antitoxin is of use in the treatment of scarlet fever. No antitoxin or other serum at present available has any direct action on septic

158 O'Brien: *Discussion on the Serum Treatment of Scarlet Fever*

complications. The early use of serum probably reduces the liability to late septic complications and reduces the length of stay in hospital, but many further observations are required.

Concentrated scarlet fever antitoxin protects rabbits against the first "toxæmia" or "septicæmia" caused by hæmolytic streptococci obtained from cases of follicular tonsillitis, puerperal fever, cellulitis, etc. The antigens of these various cultures must bear a close relationship to each other.

TABLE I (PARISH AND OKELL).—RABBITS INJECTED INTRAVENOUSLY WITH 10 C.C. OF A TWENTY-HOUR DIGEST BROTH CULTURE OF SCARLET FEVER STREPTOCOCCUS. SERUM INJECTED INTRAVENOUSLY FOUR TO SIX HOURS PRIOR TO INJECTION OF CULTURE.

	Total rabbits	Percentage living six days after injection of culture. 5 c.c. or more	1·0 c.c.	0·25 c.c.	0·1 c.c.
Normal horse serum ... ... } Concentrated diphtheria antitoxin }	20	5	—	—	—
Unconcentrated anti-streptococcus serum erysipelas ...					
,, ,, ,, strangles ...					
,, ,, ,, measles ...	29	17	—	—	—
,, ,, ,, puerperal ...					
,, ,, ,, pyogenes (Swann)					
,, ,, ,, ,, (Shilling)	17	29	0	—	—
,, ,, ,, S[1]	6	50	—	—	—
Serum from scarlet fever convalescents (Dick-negative) ...	6	50	—	—	—
Unconcentrated scarlet fever antitoxin (early stage of immunization), batch "P"	9	66	0	—	—
Unconcentrated scarlet fever antitoxin (late stage of immunization), batch "Q"	15	77	33	0	—
Concentrated scarlet fever antitoxin, batch "R"	15	88	66	33	—
,, ,, ,, ,, ,, "S"	12	100	100	66	33

TABLE II (PARISH AND OKELL).—RABBITS INJECTED WITH SERUM INTRAVENOUSLY FOUR TO SIX HOURS BEFORE INJECTION OF CULTURE INTRAVENOUSLY.

Culture, 5 to 20 c.c.	Total number of rabbits	Unprotected: No serum or normal horse serum or concentrated diphtheria serum	Protected: Streptococcus antitoxic serum: Concentrated scarlet fever, 5 c.c.	Concentrated puerperal, 5 c.c.	Unconcentrated pyogenes, 10 to 15 c.c.	Unconcentrated erysipelas, 10-15 c.c
Tonsillitis	24	0	77	—	33	—
,, ...	9	0	100	—	33	—
Lymphangitis ...	9	0	100	—	66	—
Fatal septicæmia ..	12	0	33	—	66	—
Severe septicæmia ...	15	0	66	—	—	—
Endocarditis ...	12	0	83	—	—	—
Puerperal fever (uterus) ...	25	10	83	16	0 (conc., 5 c.c.)	—
,, ,, ...	25		100	50	33 (conc., 5 c.c.)	—
,, (blood) ...	11	0	100	100	—	—
,, ,, ...	9	33	66	66	—	—
,, (uterus) ...	11	0	100	33	—	—
,, (blood) ...	11	0	100	33	—	—
Erysipelas	36	8	70 (conc., 5 to 15 c.c.)	—	—	77

Dr. F. FOORD CAIGER

said that he, too, had not had the opportunity of trying the serum, as there had not been under his care cases suitable for the purpose. When it was realized that to-day the mortality of scarlet fever was 1 per cent., it would be seen that only in a long series of cases could one find much indication of the effect of the serum in saving life, otherwise the only indication was that afforded by the rapidity with which the

[1] Broth cultures of scarlet fever streptococcus included in antigen for immunization.

symptoms cleared up, and the extent to which complications developed. Dr. Goodall had evidently noticed a rapid clearing up of symptoms in cases not necessarily severe; but with regard to the incidence of complications the results were not convincing. This impression gathered confirmation from the records quoted by Dr. O'Brien of the work of Dr. Harries, Dr. Rundle and Dr. Benson. Therefore in that respect one could not get very far. The success of the attempts made by earlier pathologists had not been greatly exceeded by the success attending the use of the present serum. He (the speaker) remembered a paper recording the work of Palmirski and Zebrowski, who, in (he believed) the late nineties, had tried a multivalent serum in a thousand cases of children in a Warsaw hospital with satisfactory results. They reported that in the mild cases it usually acted like a charm, but in the severe cases, many of which were undoubtedly septic, its good effect was only moderate. They went so far as to say that if streptococci were found in the actual circulation the serum was of no value at all. Their serum was prepared from seventeen fatal cases of scarlet fever. Moser's work, published in about 1900, achieved for the author an almost world-wide reputation; but his serum treatment had gone the way of so many others.

With regard to Dr. Goodall's statement that in certain cases in which septicæmia was present in scarlet fever the hæmolytic streptococcus of Dick was the organism found, he (the speaker) was under the impression that in those cases which had been examined it was, almost invariably, some organism other than the Dick coccus which was present in the circulation.

He believed that success with antitoxic serum to-day would chiefly be obtained in the simple form of the disease, and would consist in a shortening of the attack; and that in the toxic form, which was now rarely seen, some benefit might be anticipated. One would hardly expect that the Dick serum alone would be of much use in the septic variety of scarlet fever. In that class of case it would seem that one had to give a multivalent serum in addition.

He would briefly refer to the success he himself had obtained between twenty and thirty years ago with a serum which was sent to him from Paris by Professor Besredka, of the Institut Pasteur—a multivalent serum derived from twenty strains of scarlatinal streptococci. The Professor had sent him a large case of it, and it almost seemed as if there was enough to last for life, so large was the number of bottles of serum in 50 c.c. doses. It was obvious, however, that he could not use it in every case of scarlet fever, and he decided to give it only to patients whom he regarded as likely to die under ordinary treatment. The dosage employed was 50 c.c., repeated daily for so long as necessary, the average number of doses given being between three and four. Enough had been sent for the treatment of forty-four cases, and the ultimate mortality of those very severe cases—in each of which a fatal prognosis would not have been otherwise far wrong—had been only 36 per cent. The mortality-rate in cases in which the treatment was begun on the fourth and fifth days of the attack was 23 per cent.; when it was given two days later, the rate was 35 per cent.; and when it was not given until the ninth day the death-rate was just over 50 per cent. This was more than twenty years ago, and he (the speaker) doubted whether the treatment of scarlet fever had advanced very much further since that time.

Dr. J. D. Rolleston

said that Dr. Goodall had referred to the mild character of scarlet fever in this country, and in that connexion the following figures might be of interest. From 1874 to 1879, shortly after the hospitals of the Metropolitan Asylums Board were established, the case-mortality from scarlet fever was 13·9 per cent., which was

160 Rolleston: *Discussion on the Serum Treatment of Scarlet Fever*

exactly the figure given by Chodzko,[1] the Polish epidemiologist, of the mortality-rate in Warsaw during the first twenty-six weeks of 1926. During the following years the case-mortality in London gradually declined. For instance, in the period 1890-94 it had fallen to 6 per cent., and in 1900 it was 3 per cent. From the last Report of the Asylums Board (1925-26) it would be seen to be 1·1 per cent; while in his (the speaker's) own hospital (Western Hospital) it was 0·65 per cent. in 1925, and in 1926 it was 0·88 per cent. It seemed that now scarlet fever, as it was when described by Sydenham, was hardly worthy of the name of disease. It was interesting, as Dr. O'Brien pointed out, that the disease was more severe in the North. It was mild in France, but the mortality from the disease in this country was not so high as French writers supposed. Even so well-informed a person as Professor Teissier[2] contrasted the malignancy of scarlet fever in this country with its mild character in France. It was especially in South-East Europe that scarlet fever was malignant; in Roumania, Bulgaria and Italy the mortality from it was quite high. The figures, however, must be accepted with some caution. They were to be found in the June and July issues of the *Bulletin de l'Office International d'Hygiène Publique*, especially in the report which was drawn up by Dr. Allan Parson, of the Ministry of Health, and presented by Sir George Buchanan to the International Office.[3] It gave the morbidity and mortality figures from scarlet fever in the various countries of the world. It had been pointed out, however, that in countries with a high case-mortality there was a tendency not to include all the cases; it was rather the severe cases which were included, the milder cases being omitted.

He agreed with what Dr. Goodall had said about not giving the serum in every case of scarlet fever. In studying the literature, he found that several writers urged that this should be done, just as serum was given in practically every case of diphtheria. The concentrated form of the serum was expensive, but apart from this fact there were two objections: (1) (mentioned by Dr. Goodall) that a patient might contract serum disease, which might be more severe than an attack of scarlet fever; (2) that the patient was rendered hypersensitive for some years to come, so that if serum were needed at a future date as a prophylactic against tetanus, or for therapeutic purposes against cerebro-spinal meningitis, the reaction to it was likely to be very violent. For that reason there were only a few cases in which he (Dr. Rolleston) had used the serum. Since March, 1926, out of about 1,000 cases of scarlet fever he had had only sixty-two which he thought required the serum, and those he had divided into classes (*a*), (*b*) and (*c*). In class (*a*) there were twenty-three cases in which there appeared to be immediate and marked benefit from the serum; in class (*b*) were twenty-four cases in which the benefit, though definite, was less marked and rapid; in class (*c*) there were fifteen cases showing no benefit from it, and the deaths numbered five. Serum rash was present in twenty-six cases; in nine there was pyrexia, with some constitutional disturbance, and sometimes there was secondary adenitis and pain in the joints, such as was met with in serum sickness due to other sera.

His dosage, like that of Dr. Goodall, had varied from 10 c.c. to 30 or 40 c.c. Sometimes, but not often, the doses were repeated.

Another point had been suggested to him by Dr. O'Brien's contribution, namely, that of discharging patients earlier if they had had the serum. Was one justified in doing so without a bacteriological examination? He had had no personal experience of the bacteriology of scarlet fever, but in the *American Journal of Hygiene*, and also

[1] *Bull. Off. Internat. d'Hyg. Publ.*, 1926, xviii, 1295.
[2] *Nouveau Traité de Médecine* (Roger, Widal, Teissier), 1922, Fasc. ii, art. "Scarlatine," 1.
[3] *Bull. Off. Internat. d'Hyg. Pub.*, 1926. xviii, 612.

Section for Study of Disease in Children and Section of Medicine 161

in a German paper, it was stated that *Streptococcus scarlatinæ* persisted for a long time. According to the American observer,[1] it was found to persist at the end of three weeks, and in the case of the German observers [2] it was still persisting at the end of six weeks

Sir FREDERICK ANDREWES, O.B.E., F.R.S.

said that he had had no practical experience in the application of serum treatment to scarlet fever; but in one question he was more interested than in the treatment of scarlet fever itself, namely, that which had been brought forward in Dr. O'Brien's remarks about the overlapping of the effect of scarlatinal antitoxic serum on other streptococcal diseases. It raised a point of fundamental difficulty and importance, namely, whether there was, clinically, such a disease as scarlet fever; i.e., whether it was a sharply-defined entity, or whether it so shaded off into other forms of streptococcal infection that it was difficult to say what was scarlet fever and what was not. During the last thirty-five years, at St. Bartholomew's Hospital, it had been his (the speaker's) duty to issue a report on all cases of infectious disease arising *de novo* in the wards; and in that time he had seen, perhaps, hundreds of cases of doubtful scarlet fever which had originated in hospital; so-called "burn" scarlet fever, cases originating after operations—usually two days afterwards in children—and at the end of that long experience he was left in the gravest doubt as to where scarlet fever left off and where other forms of streptococcal infection began. And in the bacteriological evidence for the streptococcal nature of scarlet fever there was the same difficulty; was it always one particular kind of recognizable streptococcus which caused scarlet fever? In a recent paper Dr. Griffith, of the Ministry of Health Laboratories, had stated his conclusion that at least three different serological types of streptococcus were obtainable from the throats of scarlet fever patients; and the two common in this country were not those which seemed commonest in the United States. But he (the speaker) did not wish to put forward a serological classification of streptococci from the point of view of agglutination as necessarily covering the ground in the diagnosis of scarlet fever. The important thing which had emerged from recent studies in scarlet fever was the recognition that it must be looked upon as pre-eminently a toxic disease. People talked about "toxic scarlet fever" twenty years ago, but that was very different from being able to isolate the toxin of scarlet fever, study it in the laboratory and immunize animals against it. Might there not be a number of serological races of the coccus, all forming one common toxin, as was the case with the bacilli of tetanus and gas gangrene? In the case of the diphtheria bacillus there were a number of races serologically recognizable by agglutination, but forming a common toxin. And might not that toxin be produced by other forms of streptococcus than those obtainable from the scarlet fever throat? The facts which Parish and Okell had published seemed to afford some evidence that such was the case.

It would be interesting to see how far the concentrated scarlet fever antitoxin which Dr. O'Brien was preparing would prove efficacious in conditions allied to scarlet fever. One of the workers on streptococci in his (Sir Frederick's) laboratory contracted what, clinically, was typical acute rheumatic fever, in the summer of 1926. Some of Dr. O'Brien's concentrated anti-scarlet fever serum was administered to her, and, apparently, with strikingly beneficial result. When, later, she had a relapse, a dose of the serum was administered, and in four hours the temperature had returned to normal and the pain had left the joints.

There was much yet to learn about the toxins of scarlet fever and the streptococci generally, and it was along those lines that future advance was likely to be made.

1 E. E. Nicholls, *Amer. Journ. Hyg*, 1927, vii, 84.
2 V. Friedemann and H. Deicher, *Deutsche med. Wochenschr.*, 1926, lii, 2147.

162 Joe—Martin: *Discussion on Serum Treatment of Scarlet Fever*

Dr. ALEXANDER JOE

said he wished to touch on one or two points particularly in regard to the types of the disease.

He agreed that there had not been much opportunity in London of clinically estimating the value of this serum. The disease in London was mild in comparison with what it was in the North—in Edinburgh, for instance. In London he (Dr. Joe) had not been able to show to his students a single case of the septic type. Other complications such as otitis, adenitis, and arthritis seemed to be very similar, but in five months he had not seen a true case of scarlatinal nephritis. For that reason the evidence of Dr. Benson probably carried much weight.

With regard to serum sickness, he had not seen a very severe type of scarlet fever in London, but, until he came to London, he had never realized what serum sickness was. He did not know whether this was due to greater sensitiveness on the part of the children in London, or to the type of serum provided, but in the North there were not so many cases of serum sickness, nor was there such an extreme degree of it when it did occur. This applied, of course, particularly to the treatment of diphtheria. Even so, he (the speaker) did not regard the possibility of serum sickness as a contra-indication for the use of scarlatinal antitoxin in cases requiring it, especially when a concentrated serum was available.

Another interesting point concerned the efficacy of the older serum. He and his colleagues had used it in the very septic cases, but he realized now that the reason why better results had not been obtained was probably that it was given too late. Soon after the Schultz-Charlton work was published, someone had used this old serum, which had produced a definite degree of blanching, thus proving that it contained a specific antibody.

With regard to overlapping, the puerperal serum which Dr. O'Brien had given him had produced in one case a fair amount of blanching in a typical scarlet fever rash. About the time when the anti-scarlatinal serum was first produced he (the speaker) had injected it intracutaneously in the track of a spreading erysipelas, but it did not hold up the spread of the erysipelas. On the other hand, he had isolated a streptococcus from a case of erysipelas which gave the typical reactions of the Dick toxin in a 1 in 1,000 dilution. It produced a high percentage of positive reactions in early scarlatina, and a high percentage of negative reactions in the late days of the disease.

Referring to Sir Frederick Andrewes' remark as to scarlet fever being a clinical entity, he (Dr. Joe) had no doubt that it was such, but he had once heard an ear-and-throat surgeon say that sometimes while the patients on whom he had performed tonsillectomy were contracting scarlet fever, the patients on whom he had performed mastoid operations were beginning to suffer from erysipelas. He (the speaker) did not know whether this was more than a clinical impression, but definite evidence had been produced that evening by Dr. O'Brien of a certain overlapping in the antigenic qualities of these organisms, and it was also possible that the mechanism of infection determined to some extent the clinical picture.

Dr. C. J. MARTIN, F.R.S.,

asked whether any colleagues had met with an epidemic spread of any other form of streptococcal infection, such as occurred in scarlet fever.

Dr. J. E. McCartney

said that one point raised was as to how long the so-called *Streptococcus scarlatinæ* persisted in the throat. One had visions of people being regarded as carriers, just as in diphtheria, and it was necessary to determine what the infectivity of scarlet fever was before clinicians asked bacteriologists to examine the throats of patients with a view to discharge.

He had always thought there was an overlapping of the group of streptococci. Quite recently one of the maids in a hospital had been suffering from scarlet fever. She had partially recovered from that when she had contracted erysipelas. The temperature became normal, and then pyæmia developed. A hæmolytic streptococcus was isolated from the blood, and the clinician wished to know whether the erysipelas or the scarlatinal streptococcus was responsible for the complication. He (Dr. McCartney) could not answer such a question, because little was known about the inter-relationship of these streptococci. Work must be done on that before the degree of infectivity of these cases of scarlet fever could be determined. Perhaps information would be obtained if a study were made of the organisms in those cases which failed to respond to serum treatment. The scarlet fever serum did not influence certain types of cases, and if those types were studied more and the serological characters observed, another serum could perhaps be made which would exercise a beneficial effect on the cases it was desired to save.

Dr. H. J. Parish

said that further experiments carried out by Dr. Okell and himself appeared to suggest the identity of hæmolytic streptococcal toxins. Rabbits could be killed by the intravenous injection, not only of scarlet fever streptococci, as mentioned by Dr. O'Brien, but also of toxin; large doses of toxin, however—(20 to 40 c.c.)—were required to ensure deaths overnight. If antitoxin were given from four to six hours before injecting the toxin, the rabbits survived. Such experiments had only been possible with scarlet fever toxin, as erysipelas and puerperal fever toxins tended to be much weaker, and there was a limit to the volume of toxin broth one could inject into the rabbit's circulation.

Yesterday he (the speaker) had injected three Dick-positive and two Dick-negative individuals with 1 in 1,000 scarlet fever and 1 in 250 erysipelas and puerperal fever toxins. In each Dick-positive individual the scarlet fever toxin gave the best reaction, the puerperal next, and the erysipelas least. In the Dick-negative persons no reactions occurred with any of the toxins. These experiments on rabbits and in man suggested only quantitative differences between the three toxins.

To parallel the failure of antitoxin to prevent the septic complications of scarlet fever: large amounts of serum did not prevent the development of arthritis in rabbits injected with cultures of hæmolytic streptococci. In practically all the rabbits which were protected against the initial phases of the infection, joint lesions developed at the end of the first week. At first these were slight, but later became very severe; there was usually pus in the joints and neighbouring muscles from which one could recover hæmolytic streptococci.

Dr. Goodall (in reply)

said that he was glad to hear, through Dr. O'Brien, that his (the speaker's) favourable impression of the serum had been confirmed by observers of wider experience. He was doubtful whether the use of the serum would shorten the stay of the patients in hospital to less than four weeks. He had been discharging mild cases at the end

of that period for the last twenty years. If the serum cut short severe cases and prevented complications, a larger number of patients would be discharged after a month.

As regarded the Russian work, Gabritchewsky had used as a prophylactic in certain Russian villages a vaccine consisting of the scarlatinal streptococci, together with the broth in which they had been grown, and, it was stated, with success. The result of this work had not become known in this country because it had been published in Russian. Gabritchewsky died before he had completed his observations, and the war had turned our minds to other matters.

In answer to Sir Frederick Andrewes, there were borderland cases, difficult to diagnose, in every acute infectious disease; but the syndrome, sore throat, punctate erythema and fever, known as scarlet fever, was very definite. That disease gave rise to similar cases and not to others, such as erysipelas. Longstaffe had shown, many years ago, that scarlet fever, erysipelas, puerperal fever and pyæmia were closely connected epidemiologically.

Referring to Dr. Martin's question, there were outbreaks of septic sore throat which were neither due to scarlet fever nor to diphtheria. Some of them were milk-borne epidemics. He would instance the outbreaks in Lincoln, Hackney, and some of the large cities of the United States, for example, Chicago. All were due to streptococcal infections.

He was interested to hear from Dr. Joe, who had now had experience of scarlet fever in both Edinburgh and London, that the disease was more severe in the former city than in the latter. Possibly that was a reason for the more definite results obtained in Edinburgh. The antidiphtheria serum used in the Asylums Board Hospitals was unconcentrated, and more frequent and severe serum rashes were met with than in Edinburgh, where concentrated serum had been used.

Dr. O'Brien (in reply)

said that Dr. Caiger's account of results obtained by the use of serum some years ago made him (the speaker) feel that he had failed to make his point of reconciling what had been done in the past with what was known to-day. The anti-streptococcus serum which had been made for twenty years past apparently protected 50 per cent. of rabbits in the Parish-Okell test. It was practically certain that the serum Moser used contained antitoxin. None of that was available now, but one could test the material made a few years ago. The Dick serum had been first made in April, 1924, but we had to-day a serum made before that date, by the old methods of Moser and others, and this serum clearly protected rabbits against scarlet fever streptococci. The case was parallel to the time, in 1894, when diphtheria serum was first introduced. In the hands of many people it was a failure, but in some hospitals it produced dramatic effects. The explanation was that the serum available in this country was a very low-grade serum. It cured some cases, but it did not contain enough antitoxin to be generally convincing.

With regard to the bacteriology of this disease, Gordon, of Chicago, had recently reported that of 100 scarlet fever cases, sixty-two among the control group who had not been treated with serum, and thirty-one who had been so treated, had the hæmolytic streptococcus of scarlet fever in the throat on the twenty-eighth day. Scarlet fever patients had apparently been discharged from hospitals with hæmolytic streptococci in their throats for years past, but they were not acutely infectious, or "return" cases would more often occur.

With regard to Dr. Martin's question, military records showed that there had been epidemics of sore throat without a rash in groups of soldiers confined to

barracks, and that these had spread over large groups of men. One such had occurred in the South African war.

Reverting to the old work on this subject, Dr. Gabritchewsky's death, in 1905, was to be regretted. It was most refreshing to read his work and to note the logical way in which he passed from one step to another. He had produced a highly successful anti-scarlet fever vaccine.

With regard to the cases mentioned by Dr. Parish, the septic element of scarlet fever was the important one. The deeper one went into it the more difficult it became, and the more clearly it was seen that fascinating problems lay ahead. Possibly there was an overlapping in, or even identity of, the antigens of all the hæmolytic streptococci, but the baffling thing to-day was the occurrence of later septic phenomena. In the rabbits experimented upon, the first attack of the streptococcus was neutralized by the serum, and the protected rabbits were alive and well after the control rabbits were dead, but later joint lesions had developed. This curious paradox was first recorded, in connexion with pneumonia, by Mair and Gaskell. One could immunize a rabbit with dead pneumococci at first, then with the living pneumococci, and the rabbit's serum would protect a mouse against many lethal doses of pneumococcus; endocarditis and other pneumococcal lesions developed in the rabbit itself. Until a means of preventing this late arthritis in the rabbits was discovered, it would not be possible to avoid these serious complications. Dochez had sent to him (the speaker) some of his antibacterial serum, and he had tried that and other sera supposed to be antibacterial and containing a large amount of agglutinin, but those sera had not saved the rabbits from this late arthritis. The worker who could solve the problem of preventing these complications would earn a great debt of gratitude.